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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/381,497	02/17/2000	DAVID J. FITZGERALD	015280-317100US	4036

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EXAMINER	
TUNGATURTHI, PARITHOSH K	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 04/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/381,497	FITZGERALD ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *20 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7-11,13,14,16,17,22-26,29-32 and 50-72* is/are pending in the application.

4a) Of the above claim(s) *57-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 7-11, 13-14, 16-17, 22-26, 29-32, 50-56 and 70-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/20/2006 has been entered.

2. Claims 1-4, 7-11, 13-14, 16-17, 22-26, 29-32 and 50-72 are pending.

Claims 8, 9, 54 and 56 have been amended.

Claims 57-72 have been newly added.

Since claims 57-69 are method claims and the product claims were previously elected for examination, Claims 57-69 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

3. Claims 1-4, 7-11, 13-14, 16-17, 22-26, 29-32, 50-56 and 70-72 are under examination.

4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

5. This office action contains new grounds of rejection.

Response to Arguments

6. The rejection of claims 50-56 and the newly added claims 71 and 72 under 35 U.S.C. 112, first paragraph is maintained. The response filed on 3/20/2006 has been carefully considered but is deemed not to be persuasive.

Applicants argue that the claims do not recite a sequence that is 95% identical to the CDRS of SEQ ID NO:2, instead the claims recite that the VH and VL regions have the CDRS of SEQ ID NOs. 2 and 4 and have the recited percent identity to SEQ ID NOs. 2 and 4; and accordingly, the Examiner's argument that one of skill in the art could not predict that an antibody that has 95% identity to SEQ ID NO:2 or 4 with alterations in the CDRS would have the required binding specificity is not applicable to the instant claims.

In response to the above arguments, the applicant is reminded that the claim recite "a recombinant immunoconjugate.....which heavy chain comprises the CDRs of SEQ ID NO:2 and is at least 90% identical to SEQ ID NO:2.....which light chain comprises the CDRs of SEQ ID NO:4 and is at least 90% identical to SEQ ID NO:4". Thus, the claims even though recite that the heavy and the light chains comprise the CDRs of SEQ ID NO:2 and SEQ ID NO:4, the claims also recite that the heavy and light chain have at least the percent identity of the entire length of SEQ ID NO:2 and SEQ ID NO:4. Since the percent identity is representative of the entire length

of SEQ ID NO:2 and SEQ ID NO:4, and these sequences comprise CDRs, the claims can be interpreted such that the claims are drawn to a recombinant immunoconjugate having at least 90% identity to the CDRs or the framework region or both within SEQ ID NO:2 and SEQ ID NO:4. Due the indefinite nature of the instant claims (please see below in new grounds of rejection), the rejection of claims 50-56 under 35 U.S.C. 112, first paragraph is maintained.

7. The rejection of claims 1-4, 7-11, 13-14, 16-17, 22-26, 29-32, 50-56 and the newly added claims 70-72 under 35 U.S.C. 103(a) as being unpatentable over Ghetie et al (Cancer Res. 51:5876-5880, 1991) and further in view of Shen et al (Int. J. Cancer 42:792-797, 1988) and Reiter et al (Biochemistry 33:5451-5459, 1994) and Kuan et al (Biochemistry 35:2872-2877, 1996, Abstract published 2/1/96) and Orlandi et al (Proc. Natl. Acad. Sci. USA, 86:3833-3837, 1989), Cabilly et al (U.S Patent 4816567, issued 3/89), Boss et al (U.S Patent 4816397, issued 3/89), Robinson et al (U.S. Patent 5618920, filed 4/94), Ward et al (Nature 341:544-546, 1989), and Huston et al (U.S. Patent 5258498, issued 11/93) is maintained.

The response filed on 3/20/2006 has been carefully considered but is deemed not to be persuasive.

Applicants argue that "The claimed compositions and methods are directed to the treatment of B-cell malignancies, e.g., B-cell lymphoma, hairy cell leukemia and chronic lymphocytic leukemia. The passage referred to by the Examiner in Reiter et al states that "[s]uch single-chain Fv's (scFv's) can retain specificity and affinity. . . ." . This

merely states that scFv's retain affinity, it does not teach that the affinity is equivalent to that of the parent Ig molecule. In addition, the reference provides no teaching or suggestion that a toxin-dsFv conjugate can retain the binding affinity of a parent IgG" (page 8 of response, in particular). In addition, the applicant argues that the comparison of the improves binding affinity of dsFv immunotoxins in Reiter et al appears to be based on a comparison of dsFv-toxin to scFv toxin, and that Reiter et al in fact show that it is uncommon that the dsFv toxin conjugate molecules retain the binding affinity of the parent IgG molecules.....and that the applicants assertion of unexpected and superior results of the claimed compositions is proper (page 9, 2nd paragraph). The applicants further argue that "the examiner has provided no evidence that the degree of efficacy as shown in the Declaration by Dr. Fitzgerald could have been expected from prior art" (page 9, 3rd paragraph).

In response to the above argument, it is to be noted that the claims under examination are drawn towards a product and not the method of use of the product. Thus, the method in which the product is used is considered irrelevant for the examination of the product. Hence the above argument that the claimed compositions and methods are directed to the treatment of B-cell malignancies is not found persuasive. Further, the applicant is reminded that under 35 U.S.C. 103 it is only necessary to establish motivation to combine the references, and that the ordinary skilled artisan would have reasonable expectation of success being able to produce the invention. Hence, in response to the applicants arguments that "does not teach that the affinity is equivalent to that of the parent Ig molecule" and "the reference provides no

teaching or suggestion that a toxin-dsFv conjugate can retain the binding affinity of a parent IgG", the applicant is reminded of the teachings of Reiter et al.

Reiter et al (Biochemistry) teach that they have optimized the design and the purification scheme so the yields of dsFv-active immunotoxins are consistently higher than those of the scFv-toxins and the increased yield is due to the decreased tendency of properly folded immunotoxins to aggregate (see abstract). Thus, it would not have been surprising to get higher expression or production of the dsFv-toxins.

It is noted that the declaration of Dr. Fitzgerald states that "The RFB4dsFv, not only express well, but also retains the binding specificity and affinity of RFB4 IgG. This is unusual and surprising, not only in contrast to LL2-containing immunoconjugates, but in comparison to many recombinant immunotoxins. Typically, binding affinity is lowered in comparison to the parent antibody" (paragraph 8 of the declaration submitted on 03/15/2004). The declaration states that the dsFv antibody retains the binding specificity and affinity of IgG, but not better than IgG. Hence the applicants arguments in this regard are not found persuasive. However, Reiter et al teach "that dsFv's have at least the same binding properties as scFv's, and in some cases they may be better" (see abstract) and that scFv can retain the specificity and affinity of IgG (see page 5451). Hence it can be expected that the dsFv's can retain the specificity and affinity of IgG. The applicant is respectfully requested to provide the evidence as to how it is surprising to expect that dsFv's can retain the specificity and affinity of IgG. Thus, The declaration of Dr. Fitzgerald is respectfully considered, however it does not satisfy the unobviousness or the unpredictability of the claimed invention as stated by the applicant

because the specific antibody including the further limitations as claimed are clearly known in the art.

Further, in response to the applicants argument that "the examiner has provided no evidence that the degree of efficacy....could have been expected from prior art", it should be noted that Reiter et al (Nature Biotech cited by applicant) teach 4 out of 8 dsFv-immunotoxins had improved binding affinity (see page 1243, left column) and shows better cytotoxicity for the dsFv as compared to the scFv and better expression yields (see Table 1) and better stability (see Table 2). In addition, because the dsFv have superior characteristics over the scFv they would obviously be chosen over scFv and would have been expected to have the high degree of efficacy and promising results as the applicants argue. Further, Reiter et al teach that the dsFv-immunotoxins (and dsFv's alone) might be more useful thatn scFv's in clinical and other applications (abstract in particular).

The applicants also argue that Shen et al teach that the Fab' fragment for RTB4 had a lower binding affinity relative to the intact antibody and that the Fab' molecules when conjugated to a toxin moiety, the ricin A chain, do not retain the affinity of the parent R1784 antibody and thus, prior art RFB4 immtmotoxin compounds do not exhibit the particular benefit of the currently claimed compositions (page 9 1st paragraph).

In response to the above arguments, the applicant is reminded that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation

to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Further, Shen et al teach that the Fab'-RFB4 bound 1 .2 to 3.5 times more stronger than other Fab' fragments and the potent cytotoxic activity of the RFBM-AS appears to derive from their superior binding affinity and the art recognizes the superiority of this antibody.

Further, the newly added claims recite a pharmaceutical composition comprising an effective amount of the recombinant immunoconjugate. The "pharmaceutical composition" is considered as an intended use of the conjugate and hence is not give any patentable weight, and thus the claims are considered as the product claims. Hence, the newly added claims 70-72 are rendered obvious over the references cited above.

Therefore, one of skill in the art would have been motivated to and had a reasonable expectation of success to have produced the claimed invention.

New Grounds of Rejection:

8. Claims 50-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 50 and 56 are indefinite for reciting "a recombinant immunoconjugate.....which heavy chain comprises the CDRs of SEQ ID NO:2 and is at least 90% identical to SEQ ID NO:2.....which light chain comprises the CDRs of SEQ ID NO:4 and is at least 90% identical to SEQ ID NO:4". It is not clear as to what the applicant means by "heavy chain comprises the CDRs of SEQ ID NO:2 and is at least 90% identical to SEQ ID NO:2" OR "light chain comprises the CDRs of SEQ ID NO:4 and is at least 90% identical to SEQ ID NO:4". Does the applicant mean that the heavy and light chains comprise the CDRs of SEQ ID NO:2 and SEQ ID NO:4, and the framework regions which are 90% identical to the framework regions of SEQ ID NO:2 and SEQ ID NO:4? OR that the heavy and light chain regions comprise CDRs that are 90% identical to the CDRs within SEQ ID NO:2 and SEQ ID NO:4? OR that the heavy and light chains are 90% identical to the entire length of SEQ ID NO:2 and SEQ ID NO:4, respectively? As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims. Accordingly, the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Conclusion

9. No claims are allowed

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is

571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

11. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
Parithosh K. Tungaturthi, Ph.D.
Ph: (571) 272-8789

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER